0022-5347/99/1623-0659/0
THE JOURNAL OF UROLOGY
Vol. 162, 659–664, September 1999
Printed in U.S.A.

CLINICAL AND GENETIC CHARACTERIZATION OF PHEOCHROMOCYTOMA IN VON HIPPEL-LINDAU FAMILIES: COMPARISON WITH SPORADIC PHEOCHROMOCYTOMA GIVES INSIGHT INTO NATURAL HISTORY OF PHEOCHROMOCYTOMA

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ABSTRACT

Purpose: Families with von Hippel-Lindau disease have variable risk of pheochromocytoma. Patients with von Hippel-Lindau disease and pheochromocytoma identified by screening can have no characteristic signs or symptoms. Families with von Hippel-Lindau disease were screened and followed to describe the natural history of von Hippel-Lindau pheochromocytoma, and to correlate these findings with von Hippel-Lindau germline mutation.

Materials and Methods: Between 1988 and 1997, 246 individuals with von Hippel-Lindau disease were identified (von Hippel-Lindau group). Between August 1990 and June 1997, 26 consecutive patients with sporadic pheochromocytoma were evaluated (sporadic group).

Results: A total of 64 patients with von Hippel-Lindau disease had manifestations of pheochromocytoma, including 33 newly diagnosed during screening at the National Institutes of Health and 31 previously treated (93 adrenal and 13 extra-adrenal pheochromocytomas). Germline von Hippel-Lindau gene missense mutation was associated with extra-adrenal pheochromocytoma, younger age at presentation and the only patient with metastases. Of the 33 newly diagnosed patients with von Hippel-Lindau disease 4 had pheochromocytoma 2 times (37 pheochromocytomas) during followup. Of these pheochromocytomas 35% (13 of 37) were associated with no symptoms, normal blood pressure and normal catecholamine testing. Comparison of urinary catecholamines in the von Hippel-Lindau and sporadic groups demonstrated increased epinephrine, metanephrines and vanillylmandelic acid in the sporadic group. Analysis of urinary catecholamine excretion in the von Hippel-Lindau and sporadic groups together demonstrated a correlation between tumor size, and urinary metanephrines, vanillylmandelic acid, norepinephrine, epinephrine and dopamine. In 12 patients without signs or symptoms of pheochromocytoma 17 newly diagnosed pheochromocytomas were followed for a median of 34.5 months without morbidity. Median tumor doubling time was 17 months.

Conclusions: Von Hippel-Lindau gene missense mutation correlated with the risk of pheochromocytoma in patients with von Hippel-Lindau disease. These findings support a von Hippel-Lindau disease clinical classification, wherein some families are at high risk for manifestations of pheochromocytoma. Von Hippel-Lindau disease pheochromocytomas identified by screening were smaller and less functional than sporadic pheochromocytomas.

KEY WORDS: pheochromocytoma, Hippel-Lindau disease, diagnosis, genetics

Von Hippel-Lindau disease is an autosomal dominant disorder in which affected individuals are at risk for pheochromocytomas, retinal angiomas, central nervous system hemangioblastomas, endolymphatic sac tumors, epididymal cystadenomas, renal cysts and carcinomas, and/or neuroendocrine tumors and cysts of the pancreas.[1–3] Studies of families with von Hippel-Lindau disease have led to a clinical classification system based on development of different tumors.[4] Families without pheochromocytoma are classified as type 1 and those with pheochromocytoma as type 2. Von Hippel-Lindau disease type 2 is divided in 2A based on the presence of renal cancer or type 2B by the absence of renal cancer. This variation in risk of pheochromocytoma is a consequence of different von Hippel-Lindau disease germline mutations.

Accepted for publication April 9, 1999.

Von Hippel-Lindau disease type 2, families with pheochromocytoma, is most frequently associated with a missense mutation of the von Hippel-Lindau gene.[4,5] Missense mutations consist of deoxyribonucleic acid base substitutions which result in a full length von Hippel-Lindau peptide with an amino acid substitution. Mutations in codon 167 have been observed to occur frequently in 43% of affected members of families with von Hippel-Lindau disease type 2.[4]

Reports of clinical behavior of von Hippel-Lindau disease pheochromocytoma have indicated that patients can be normotensive[6] and some are asymptomatic.[7–9] We summarize the clinical and genetic findings in a well characterized group of patients with von Hippel-Lindau disease with pheochromocytoma (von Hippel-Lindau group). These findings are compared to those of a group of patients with sporadic pheo-

chromocytoma (sporadic group). These observations provide insight into the development of pheochromocytoma in patients with von Hippel-Lindau disease, and the natural history of pheochromocytoma in patients with von Hippel-Lindau disease and sporadic pheochromocytoma.

MATERIALS AND METHODS

Study subjects and initial National Institutes of Health (NIH) screening. Between December 1988 and August 1997, 596 patients at risk for von Hippel-Lindau disease from 143 unrelated families with von Hippel-Lindau disease underwent comprehensive screening for manifestations of the disease. A total of 113 families had von Hippel-Lindau gene germline mutations identified. Available family members older than 10 years were evaluated clinically with history and physical examination, ophthalmological examination, pre-contrast and post-contrast magnetic resonance imaging (MRI) of the head and spine, contrast enhanced abdominal computerized tomography (CT) (patients older than 20 years or children suspected to have pheochromocytoma), abdominal ultrasound, scrotal ultrasound, and 24-hour urine collection for norepinephrine, epinephrine, metanephrines, vanillylmandelic acid (VMA) and dopamine. Further testing included abdominal or chest MRI, metaiodobenzylguanidine (MIBG) scintigraphy, plasma catecholamines, glucagon stimulation and/or clonidine suppression testing. Affected patients had 2 or more von Hippel-Lindau disease related tumors, or 1 or more with a family history characterized by von Hippel-Lindau disease tumors.

Cases of von Hippel-Lindau disease with masses in the adrenal glands, sympathetic chain or organ of Zuckerkandl on abdominal CT or MRI were defined as having pheochromocytoma and all tests were correlated with these abdominal studies. In 54 patients 91 pheochromocytomas were pathologically confirmed. Of the 10 patients without pathological confirmation 6 had elevated catecholamine production or uptake on MIBG scintigraphy.

Contiguous pheochromocytoma MIBG were scored together for correlation of uptake with tumor size. One patient with von Hippel-Lindau disease with metastatic pheochromocytoma was not included in correlations with catecholamine excretion. Correlation of tumor size with catecholamine excretion was performed in newly diagnosed von Hippel-Lindau disease pheochromocytoma using the Spearman rank correlation test, except for epinephrine when the Cox model score test with ranked data was used to include tumors with levels below the threshold of detection. Statistical software used for analyses.

Catecholamine determination and testing. Elevated urinary catecholamine excretion was defined as greater than 2 times the upper reference level (table 1). Elevated plasma catecholamines were defined as greater than 2 times the upper reference level (508 pg./ml. norepinephrine, 99 pg./ml. epinephrine). Glucagon stimulation and clonidine suppression tests were generally performed sequentially at the outpatient clinic.[10,11] A tripling in plasma epinephrine or norepinephrine from a baseline less than 2 times the upper limit of normal constituted a positive glucagon stimulation test.[10,12,13] Clonidine suppression was considered positive for pheochromocytoma if elevated basal plasma catecholamine levels did not decrease to the normal range.[10,12,13]

Followup after initial screening. Patients with pheochromocytoma identified by screening but without elevated catecholamine production were followed at 6-month to yearly intervals with imaging studies, urinary catecholamines, plasma catecholamines and/or stimulation or suppression tests. Surgery was recommended when pheochromocytoma function, MIBG scintigraphy uptake or size greater than 3.5 cm. was demonstrated. Patients were screened within 6 months after surgery with abdominal CT and urinary catecholamines. Thereafter, patients without pheochromocytoma were reevaluated every 1 to 2 years. Family history and record review were obtained to evaluate tumor sites and recurrences in screened patients and deceased or unavailable family members not evaluated at the NIH.

Germline von Hippel-Lindau gene mutation analysis was performed as previously described.[4,14] Some mutations have been previously reported (table 2).[4] Families with von Hippel-Lindau disease type 2A had at least 10 affected family members involving 3 generations available for analysis during at least 10 years. Families with von Hippel-Lindau disease type 2B with pheochromocytoma had at least 1 family member with renal cell carcinoma (table 2) or a germline mutation associated with renal carcinoma in the literature.[4]

Control group. Between August 1990 and June 1997, 26 consecutive patients underwent surgical resection of sporadic pheochromocytoma at the NIH. These patients had no personal or family history, physical findings or imaging findings compatible with familial pheochromocytoma, von Hippel-Lindau disease or multiple endocrine neoplasia type 2. Genetic testing for germline mutations in similar patients has rarely been informative.[15,16]

RESULTS

Von Hippel-Lindau disease patient population. A total of 246 patients were clinically affected with von Hippel-Lindau disease. Of the patients 64 (26%) from 38 families had manifestations of pheochromocytoma, including 33 newly diagnosed during screening studies and 31 treated before screening at NIH. In 4 patients pheochromocytoma was noted 2 different times during followup at NIH. A total of 25 women and 39 men (62 white, 1 Hispanic, 1 black) with pheochromocytoma were identified.

In the 64 patients with von Hippel-Lindau disease and pheochromocytoma 88% of tumors (93 of 106) were adrenal and 12% (13 of 106) were extra-adrenal (table 3). One patient (1.6%) had widespread pulmonary and liver metastases. Of the 64 patients 12 (19%) had 16 new pheochromocytomas a median of 4.0 years (range 1.0 to 20) after the first pheochromocytoma. Asynchronous bilateral adrenal pheochromocytoma occurred in 7 patients. Of these patients 3 had recurrent pheochromocytoma in the adrenal remnant 8 to 17 years after partial adrenalectomy.

Of 36 family von Hippel-Lindau germline mutations 27 (74%) were missense mutations (table 2). In contrast, in a comparison group of 77 families with von Hippel-Lindau disease without pheochromocytoma 25 (32%) had germline missense mutations (2-tailed Fisher's exact test $p < 0.0001$). These findings support and extend those of Chen et al, with missense mutations more frequently seen in families with pheo-

TABLE 1. *Urinary catecholamines and catecholamine metabolites in von Hippel-Lindau disease and sporadic pheochromocytoma*

Variable	Von Hippel-Lindau Group		Sporadic Group		Normal Ranges
	No. Pts.	Median Value (range)	No. Pts.	Median Value (range)	
Epinephrine	27	6.5 (1–14)	16	14 (less than 5–270)	0–20 μg./24 hrs.
Norepinephrine	31	159 (19–844)	18	393 (33–5175)	15–80 μg./24 hrs.
Metanephrines	29	1.3 (0.3–4.5)	24	5.2 (1.4–46)	0–1.2 mg./24 hrs.
VMA	31	7.6 (2.7–15.9)	25	19.3 (7.9–145.6)	0–7.9 mg./24 hrs.
Dopamine	31	267 (132–434)	17	342 (119–1190)	65–400 μg./24 hrs.

TABLE 2. *Analysis of von Hippel-Lindau gene mutations in families with von Hippel-Lindau disease and pheochromocytoma*

Family No.	Mutated Nucleotide	Resulting Base Change	Amino Acid Change	No. Tumors Found in Family Members/Total No. Members Evaluated					
				Pheochromocytoma	Renal Ca	Central Nervous System Hemangioblastoma	Retinal Angioma	Cysts	Pancreatic Neuroendocrine Tumor
				Type 2A					
3127	505	T to C	Tyr to His	16/29	0/29	10/29	16/29	2/29	
3788	505	T to C	Tyr to His	3/7	0/7	1/7	3/7	0/7	
				Type 2B					
5036	Not determined			1/4	2/4	4/4	2/4	2/4	
6108	Not determined			2/2	1/2	0/2	2/2	0/2	
3158	393	G deleted	Frameshift	1/4	3/4	4/4	2/4	2/4	Localized
4578	446	A to G	Asp to Ser	4/8	7/8	5/8	3/8	2/8	
6100	543, 544	CA to TT	Ser to Cys	1/4	0/4	3/4	1/4	1/4	
6101*	547	T to C	Tyr to His	1/1	0/1	0/1	1/1	0/1	
4409	553	G to C	Gly to Arg	1/2	2/2	1/2	2/2	2/2	Metastatic
6102	553	G to C	Gly to Arg	1/3	2/3	3/3	3/3	0/3	
4577*	570	C to G	Phe to Leu	2/3	1/3	1/3	1/3	0/3	
4885*	694	C to T	Arg to stop	1/1	1/1	1/1	0/1	1/1	
1112	694	C to T	Arg to stop	1/1	0/1	1/1	1/1	0/1	
4942	695	G to A	Arg to Gly	7/8†	0/8	3/8	2/8	0/8	
3948	698	G to T	Cys to Phe	1/4	1/4	4/4	2/4	2/4	
4589	698	G to T	Cys to Phe	2/2	0/2	0/2	1/2	0/2	
2338	712	C to T	Arg to Trp	3/4	1/4	3/4	4/4	2/4	Localized
4332	712	C to T	Arg to Trp	5/5	0/5	3/5	3/5	1/5	Localized
4477	712	C to T	Arg to Trp	1/2	0/1	2/2	2/2	1/2	Localized
6103	712	C to T	Arg to Trp	1/1	0/1	1/1	1/1	1/1	
6104	712	C to T	Arg to Trp	2/5	1/5	3/5	1/5	1/5	
6107	712	C to T	Arg to Trp	2/2	0/2	2/2	1/2	0/2	
5958	713	G to A	Arg to Gln	5/5	1/5	1/5	1/5	0/5	
6105	713	G to A	Arg to Gln	3/6	4/6	3/6	2/6	1/6	
3493	713	G to A	Arg to Gln	2/2	2/2	2/2	2/2	1/2	Metastatic
5143	713	G to A	Arg to Gln	1/1	1/1	1/1	0/1	0/1	
6106	713	G to A	Arg to Gln	1/2	2/2	0/2	1/2	2/2	Localized
5068	713	G to A	Arg to Gln	3/3	0/3	1/3	2/3	2/3	Localized
4339	739	A deleted	Frameshift	1/4	4/4	1/4	1/4	1/4	
1113	776	T to C	Leu to Pro	1/2	2/2	1/2	2/2	2/2	
1056	Von Hippel-Lindau gene rearrangement			2/7	3/7	7/7	5/7	6/7	Localized
3634	11 kb 3′ Deletion detected with EcoRI DNA digest probed with group 7 cDNA			1/3	3/3	3/3	2/3	1/3	
3055	11 kb 3′ Deletion detected with EcoRI DNA digest probed with group 7 cDNA			1/8	4/8	8/8	0/8	0/8	
3103	11 kb 3′ Deletion detected with EcoRI DNA digest probed with group 7 cDNA			1/11	10/11	6/11	6/11	2/11	
4044	11 kb 3′ Deletion detected with EcoRI DNA digest probed with group 7 cDNA			1/1	1/1	1/1	1/1	1/1	Localized
				Type 2					
5959	454	C to T	Pro to Ser	1/2	0/2	0/2	2/2	1/2	Localized
	775	C to G	Leu to Val						
4783	595	C to T	Leu to Phe	3/3	0/3	0/3	1/3	0/3	Localized
3618*	699	C to G	Cys to Trp	1/1	0/1	1/1	0/1	1/1	Localized

Clinical findings in all affected members of 38 families are listed. The increased relative incidence of missense mutations in families with von Hippel-Lindau disease compared to those without pheochromocytoma was significant (2-tailed Fisher's exact test $p < 0.0001$). Pheochromocytoma was the sole manifestation of von Hippel-Lindau disease in 12 patients with von Hippel-Lindau germline mutations. Genotype-phenotype correlations have been reported previously in whole or in part in families 3127, 4409, 2338, 4477, 3493, 3103 and 3618.[4]

* New germline mutation.

† One patient in this family had metastatic pheochromocytoma.

chromocytoma.[4] Of the families with pheochromocytoma 33% (12 of 36) had mutations in codon 167 (nucleotides 712–713).

Patients with mutations at nucleotides 595 and 695 had pheochromocytoma at younger ages than those with other mutations (Wilcoxon rank sum test $p < 0.025$). Extra-adrenal pheochromocytoma was only found in families with missense mutations and was particularly associated with a nucleotide 505 mutation. The only patient with metastatic pheochromocytoma had a missense mutation and was clinical von Hippel-Lindau had type 2B disease. Bilateral adrenal pheochromocytoma was found in patients with von Hippel-Lindau disease types 2A and 2B. There was no correlation between smoking history and pheochromocytoma growth rate (data not shown).

Clinical evaluation of newly diagnosed von Hippel-Lindau disease pheochromocytoma patients at NIH. The 33 newly diagnosed cases of von Hippel-Lindau disease had pheochromocytomas 37 different times, of which 6 (16%) were associated with signs or symptoms of pheochromocytoma (table 3). Urinary catecholamine production was evaluated in the 33 newly diagnosed patients each of the 37 separate times that pheochromocytoma was identified (table 1). Functional pheochromocytomas were associated with elevation of 1 or more urinary catecholamines, including norepinephrine (18 of 21 patients, metanephrines (7), VMA (2) or total urinary catecholamines (1) (table 3). When urinary catecholamine excretion was not elevated, plasma catecholamines and glucagon stimulation were elevated once each. Of the 37 von Hippel-Lindau disease patients 13 (35%) were associated with no symptoms, normal blood pressure and normal catecholamine testing.

CT detected 49 intra-abdominal new von Hippel-Lindau disease pheochromocytomas during the 37 times pheochromocytomas were diagnosed (table 3). Chest CT revealed 2 extra-abdominal tumors. MIBG uptake was observed in 45% of pheochromocytomas (5 of 11) when urinary catecholamine excretion was not elevated. Of 14 pheochromocytomas not imaged by MIBG 12 were pathologically confirmed. Pheochromocytomas imaged with MIBG uptake were significantly larger than those with no uptake. Median volume was 11.0

TABLE 3. *Clinical findings in von Hippel-Lindau disease pheochromocytoma cases*

	No. Events/Total No. (%)
Location of tumor in all 64 pts. with von Hippel-Lindau disease	
Solitary pheochromocytoma:	
Adrenal	26/64 (40)
Extra-adrenal	1/64 (2)
Multifocal pheochromocytoma:	
Bilat. adrenal	25/64 (39)
Solitary adrenal + extra-adrenal	7/64 (11)
Bilat. adrenal + extra-adrenal	5/64 (8)
Clinical evaluation of 33 pts. with new von Hippel-Lindau disease pheochromocytoma	
Signs and symptoms:	
Hypertension	6/37 (16)
Symptoms	3/37 (8)
Catecholamine production:	
Elevated urinary catecholamines	21/37 (57)
Elevated plasma catecholamines	13/29 (45)
Pos. clonidine suppression test	10/19 (53)
Pos. glucagon stimulation test	3/26 (12)
Imaging of abdominal tumors	
CT	49/49 (100)
Ultrasound	25/39 (64)
MRI	38/38 (100)
MIBG	27/41 (66)

Extra-adrenal pheochromocytomas were in the superior aspect of the abdominal sympathetic chain in 7 patients, organ of Zuckerkandl in 3, thoracic sympathetic chain in 2 and glomus jugulare in 1.

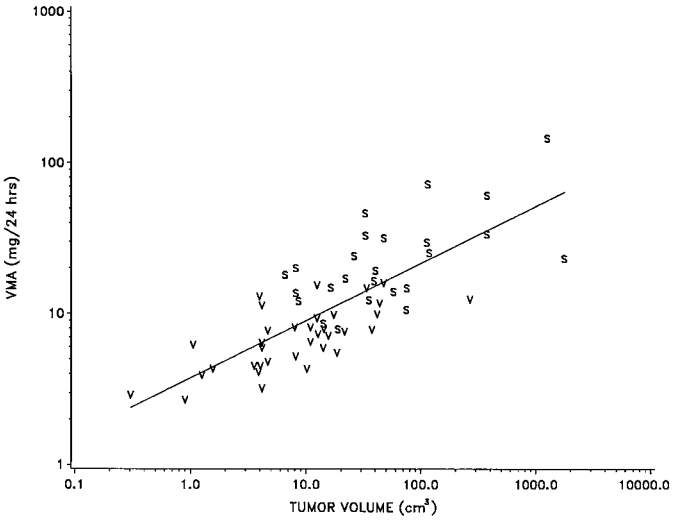

FIG. 1. Pheochromocytoma volume versus 24-hour urinary excretion of VMA in patients with von Hippel-Lindau disease (*V*) and sporadic (*S*) pheochromocytoma. Linear increase in excretion occurs with increasing size (Spearman rank correlation rho = 0.74, $p < 0.0001$, regression line included). Similar relationship exists between tumor volume, and metanephrines dopamine, epinephrine and norepinephrine excretion.

cm.^{3} (range 0.5 to 45.3) with uptake in 23 versus 1.8 cm.^{3} (range 0.3 to 12.8) without uptake in 13 pheochromocytomas (Wilcoxon rank sum test $p = 0.0006$).

A significant correlation between tumor volume, and urinary metanephrines, VMA and norepinephrine (Spearman rank correlation rho = 0.69, 0.67 and 0.70, respectively, $p < 0.0001$ each) was noted in patients with von Hippel-Lindau disease (32 to 34 evaluations in 28 to 30 patients). No association was found between tumor size and urinary epinephrine or dopamine in patients with von Hippel-Lindau disease.

Mean age at diagnosis of the first pheochromocytoma of the newly diagnosed patients with von Hippel-Lindau disease was 29.9 years (median 31.0, range 6 to 54), which was significantly younger than that of the sporadic group (39.7 years, median 39, range 25 to 73, Wilcoxon rank sum test $p = 0.0034$). The sporadic group had a higher incidence of symptoms (23 of 26 patients) and hypertension (24) than the von Hippel-Lindau group (2-tailed Fisher's exact test $p < 0.0001$ each). Von Hippel-Lindau disease pheochromocytomas were significantly smaller than sporadic pheochromocytomas (median volume 4.2 cm.^{3}, range 0.3 to 268 versus 35.4, range 5.5 to 1767, Wilcoxon rank sum test $p < 0.0001$).

Comparison of urinary catecholamines in the von Hippel-Lindau and sporadic groups demonstrated increased epinephrine (Wilcoxon-Gehan test $p = 0.0003$), metanephrines (Wilcoxon rank sum test $p < 0.0001$) and VMA (Wilcoxon rank sum test $p < 0.0001$) in the sporadic group (table 1). Smaller differences in the elevated levels of norepinephrine ($p = 0.063$) and normal levels of dopamine excretion ($p = 0.031$) were seen. Analysis of urinary catecholamine excretion in the von Hippel-Lindau and sporadic groups together demonstrated a significant correlation between tumor size, and urinary metanephrines (rho = 0.80, $p < 0.0001$), VMA (rho = 0.74, $p < 0.0001$, fig. 1), norepinephrine (rho = 0.50, $p = 0.0002$), epinephrine ($p = 0.015$) and dopamine ($p = 0.027$).

In 12 patients without signs or symptoms of pheochromocytoma 17 newly diagnosed pheochromocytomas were followed for a median of 34.5 months (range 11 to 72) with no related morbidity. Pheochromocytoma size at last followup ranged from 1.5 to 3.4 cm. Median tumor doubling time was 17 months (range 2.9 to 290). Extra-adrenal tumors had longer doubling times than adrenal tumors (Wilcoxon rank sum test $p = 0.036$). Of these 12 patients 1 had catecholamine production at initial examination and of the remaining 11, 3 had catecholamine production after 11 to 23 months. Urinary catecholamine excretion was noted in 8 patients, which did not change consistently with time. Of these 8 patients 3 had MIBG uptake, elevated plasma catecholamines, or positive glucagon or clonidine testing during followup.

The natural history of pheochromocytoma is illustrated in figure 2. This patient initially had bilateral adrenal masses, minimal elevations of urinary catecholamine excretion, normal glucagon and clonidine responses, and no uptake with MIBG. As the adrenal masses grew during the next 4 years, adrenal MIBG uptake developed and the tumors were surgically removed.

DISCUSSION

Pheochromocytoma in families with von Hippel-Lindau disease was associated most frequently with germline mis-

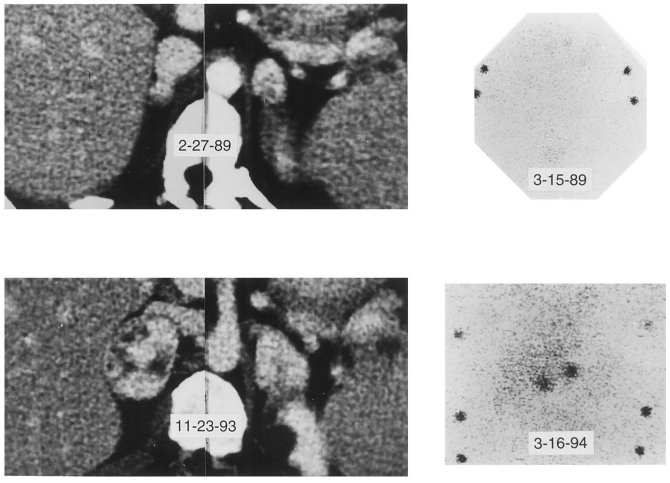

FIG. 2. Serial CT and MIBG scintigraphy show enlarging adrenal masses which developed MIBG uptake with time.

sense mutations in the von Hippel-Lindau gene. The previous association of missense mutations with pheochromocytoma as well as frequent mutation in codon 167 (nucleotide 712 and 713) reported by Chen et al in 85 families further corroborated these observations.[4] Missense mutations in 32% of families without pheochromocytoma may possibly indicate insufficient followup or mutations in areas of the gene not critical for development of pheochromocytoma.

Von Hippel-Lindau disease frequently affected by pheochromocytoma but with few other disease related findings (type 2A) has been reported as familial pheochromocytoma or multiple endocrine neoplasia type 2.[17,18] We previously identified 2 families with von Hippel-Lindau disease pheochromocytoma type 2A (3127 and 3788, table 2) associated with a nucleotide 505 mutation and are aware of 2 other families with type 2A associated with a C to G mutation at nucleotide 775 (17) and a T to C mutation at nucleotide 547.[9] In addition, 2 families not as well characterized clinically, with missense mutations at nucleotides 595 and 695, appeared to be especially at risk for pheochromocytoma (table 2). Pheochromocytoma has been associated with all of the well characterized mutations in multiple endocrine neoplasia type 2.[19–21]

Missense mutations in our patients were associated with younger age at presentation, all extra-adrenal pheochromocytomas and the only patient with metastatic disease. Thus, the characterization of pheochromocytoma in different families with von Hippel-Lindau disease validates the von Hippel-Lindau disease clinical classification scheme and has relevance for patient care.[2] Clinical evaluation of von Hippel-Lindau disease and multiple endocrine neoplasia type 2 should be performed in patients with familial pheochromocytoma, and germline testing for mutations in the von Hippel-Lindau disease and ret genes should be considered.

Clinically patients with von Hippel-Lindau disease identified by screening were younger, and had fewer symptoms, less hypertension and smaller less functional pheochromocytomas than those with sporadic tumors. In contrast, patients with von Hippel-Lindau disease not diagnosed through screening of affected families have a higher incidence of hypertension (50%).[22] These findings suggest that screening and early detection of smaller, less functional pheochromocytomas account for the "silent pheochromocytomas"[7] of von Hippel-Lindau disease, rather than a unique feature of von Hippel-Lindau disease associated pheochromocytomas that makes them less functional.

Previous evaluations of sporadic pheochromocytoma have demonstrated that elevated urinary catecholamines decrease while urinary catecholamine metabolites increase in relation to tumor size.[23,24] This change in secretion pattern apparently reflects the ability of larger tumors to metabolize epinephrine and norepinephrine to their metabolites. The small von Hippel-Lindau disease pheochromocytomas in our study were associated with lower overall catecholamine excretion and less frequent elevations of catecholamine metabolite excretion than sporadic pheochromocytomas.

The patients with von Hippel-Lindau disease also had a positive correlation between tumor size and urinary catecholamine excretion, unlike those with sporadic pheochromocytoma. When von Hippel-Lindau disease and sporadic pheochromocytomas were examined together, there was an overall linear correlation between tumor size and urinary catecholamine excretion. These data support the concept that pheochromocytomas grow from small tumors, which are initially not symptomatic or functional by conventional testing, to larger more clinically functional tumors.

In contrast to sporadic pheochromocytoma, in which it is successful,[25] the glucagon stimulation test was insensitive in patients with von Hippel-Lindau disease and small early pheochromocytoma detected through screening.[10,26] Negative glucagon stimulation tests in the presence of a positive clonidine test and symptoms or elevated urinary catecholamines have also been observed in other studies of familial forms of pheochromocytoma, including multiple endocrine neoplasia type 2.[7,25,26] Plasma metanephrines may represent a better test for pheochromocytoma[28] and are currently being evaluated.

The clinical observations of patients with von Hippel-Lindau disease and pheochromocytoma suggest guidelines for screening and treatment. Screening of high risk families should start at the earliest reported age at diagnosis, that is 4 years. Pheochromocytoma should be removed when functional, as demonstrated by urinary or plasma catecholamines, or with positive response to glucagon or clonidine testing. MIBG uptake, while suggestive of function, may not be associated with any detectable abnormality of catecholamine production. Nonfunctioning or minimally functioning tumors may be followed, especially when quality of life issues mitigate against surgery. Any patient with von Hippel-Lindau disease and signs or symptoms compatible with pheochromocytoma, or about to undergo an operation or become pregnant should be evaluated for pheochromocytoma and treated.

Bilateral adrenalectomy, as advocated by some for the treatment of multiple endocrine neoplasia type 2, would require lifelong steroid replacement with its associated morbidity and mortality.[28–31] Left in place functional von Hippel-Lindau disease pheochromocytoma can have potentially lethal consequences.[9] Partial adrenalectomy can preserve adrenocortical function but leaves a risk of local recurrence.[32] With observation of nonfunctional tumors or partial adrenalectomy,[32] patients with von Hippel-Lindau disease have been followed without morbidity and with preservation of adrenocortical function.

Courtney Holmes and Dr. David Goldstein provided plasma catecholamine determinations.

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